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REMARKS

These remarks are in response to the Office Action mailed November 20, 2003. Claims 1 to 9 and 21 to 28 are pending. Claims 5 and 21 to 28 have been canceled herein without prejudice. Applicants maintain the right to prosecute the canceled claims in any related application claiming the benefit of priority of the subject application. Claims 1 to 4 and 6 to 9 are therefore under consideration.

Regarding the Amendments

The amendments to claims 1 and 4, are supported throughout the specification or were made in order to address several informalities. In particular, the amendment to claim 1 to recite "pharmaceutical," is supported, for example, at page 20, lines 21-27. The amendment to claim 1 to recite a composition "lacking detectable adenovirus" is supported, for example, at page 23, lines 1-5. The amendment to claim 4 to recite a mutation "encoding an alanine residue in place of lysine in the fifth amino acid position from the beginning of mature F.IX" is supported, for example, by claim 5, as originally filed. Thus, as amendments to claims 1 and 4 are supported by the specification, no new matter has been added and entry thereof is respectfully requested.

I. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The rejection of claims 1 to 9 and 21 to 28 under 35 U.S.C. §112, first paragraph, as allegedly lacking an adequate written description, is respectfully traversed. The Examiner acknowledges that "Applicants arguments are persuasive insofar as the Factor IX gene has the same activity as wild-type Factor IX," but, allegedly, not for the full scope of Factors IX genes that "are more therapeutically effective" than native Factor IX protein. [see, Office Action, paragraph bridging pages 4 and 5]

Claims 1 to 9 and 21 to 28 are adequately described. Nevertheless, solely in order to Further prosecution of the application and without acquiescing to the propriety of the rejection, claims 1 and 4 have been amended as set forth above. In addition, claims 21 to 28 have been canceled without prejudice. The rejection will therefore be addressed as it may pertain to amended claims 1 to 4 and 6 to 9.

In order to satisfy the written description requirement under 35 U.S.C. §112, first paragraph, the Federal Circuit explained that "description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which constitute a substantial portion of the genus." *Reagents of the Univ. Calif. v. Eli Lilly* 119 F.3d 1559, 1568 (Fed. Cir. 1997). Although the *Lilly* court did not specify how many species constitutes a representative number, the court stated "every species in a genus need not be described in order that a genus meet the written description requirement." *Id.* Further in this regard, "Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Angstadt*, 537 F.2d, 498, 502-503 (CCPA 1976). Thus, clearly not all species of Factor IX need be described, only "a representative number." Accordingly, the statement set forth in the Office Action at page 5, that "neither the specification nor the prior art sets forth a description of the Factor IX gene such that the skilled artisan could readily envision all variants that are 'more therapeutically effective' than the native Factor IX" reflects the use of an incorrect standard for the written description requirement under 35 U.S.C. §112, first paragraph.

Here, the specification discloses five mammalian Factor IX species having blood coagulation activity, as well as a particular Factor IX variant that does not bind to collagen IV (see, for example, page 16, lines 4-15). In addition, the specification discloses that Factor IX variants, such as variants having enhanced plasma stability, can be made (page 16, lines 16-22). In this regard, methods of producing protease-resistant proteins were known in the art at the time of the invention. Furthermore, knowledge in the art regarding Factor IX structure and function, and critical and non-critical amino acid sequences for Factor IX function, was extensive at the time of the invention, as discussed in Applicants' previous response. In view of this knowledge, the skilled artisan would know of additional Factor IX sequences having blood coagulation activity. Thus, in view of the specification and knowledge in the art, one skilled in the art would certainly know of "a representative number" of Factor IX sequences having blood coagulation activity and, as such, would be reasonably apprised of the genus of Factor IX sequences that may be employed in the claimed compositions.

In sum, in view of the fact that the specification describes several Factor IX sequences having blood coagulation activity as well as a variant Factor IX in which binding to collagen IV is reduced, that other Factor IX sequences having blood coagulation activity were known in the art, and that knowledge in the art regarding Factor IX structure and function was extensive at the time of the invention such that the skilled artisan would know additional Factor IX sequences having blood coagulation activity, one skilled in the art would be apprised of a representative number of Factor IX sequences. Accordingly, an adequate written description is provided for the genus of Factor IX sequences and, as such, the rejection under 35 U.S.C. §112, first paragraph, is improper and must be withdrawn.

The rejection of claims 1 to 9 and 21 to 28 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement, is respectfully traversed. The Examiner acknowledges that the specification is enabling for "a Factor IX gene wherein Factor IX encoded by the gene has the functional properties of the wild type protein or is incapable of binding to collagen," but, allegedly, not where "the Factor IX gene is modified such that the protein encoded thereby is 'more therapeutically effective' than the wild-type gene." [see, Office Action, page 5]

Claims 1 to 9 and 21 to 28 are adequately enabled. Nevertheless, solely in order to Further prosecution of the application and without acquiescing to the propriety of the rejection, claims 1 and 4 have been amended as set forth above. In addition, claims 21 to 28 have been canceled without prejudice. The rejection will therefore be addressed as it may pertain to amended claims 1 to 4 and 6 to 9.

The test for enablement under 35 U.S.C. §112, first paragraph, is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Teletronics, Inc.*, 857 F.2d 778, 785 (Fed.. Cir. 1988), See also, *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). In ascertaining enablement, it is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d, 498, 504 (CCPA 1976).

Here, in view of the guidance in the specification and knowledge in the art, one skilled in the art could practice claims 1 to 4 and 6 to 9 without undue experimentation. As discussed

above and in Applicants' previous response, the specification discloses a Factor IX variant in which lysine is replaced with alanine in the fifth amino acid position from the beginning of mature F.IX, and in which binding to collagen IV is reduced. In view of the knowledge in the art regarding Factor IX structure and function, additional Factor IX variants in which binding to collagen IV is reduced can be made without undue experimentation. For example, the skilled artisan would know that introducing a conservative amino acid substitution in a domain of the exemplified Factor IX variant that is not critical to blood coagulation activity would produce a Factor IX variant having a different sequence from the Factor IX variant exemplified in the specification but in which binding to collagen IV is reduced. Given the knowledge of Factor IX structure and function, numerous such variants of Factor IX that differ from the Factor IX variant exemplified in the specification in which binding to collagen IV is reduced could be readily obtained. For example, the skilled artisan would produce a Factor IX sequence variant, in view of the guidance in the specification and knowledge in the art regarding Factor IX structure and function, and then confirm that the Factor IX variant had blood coagulation activity using any number of blood coagulation assays. Such assays are routine and disclosed in the specification (page 31, line 21, to page 32, line 4). Routine blood coagulation assays were also known in the art at the time of the invention (for example, page 18, line 25, to page 19, line 2, and the Walter *et al.* and Hathaway and Goodnight references cited therein). Consequently, identifying such Factor IX variants merely requires routine screening, which cannot reasonably be argued to constitute undue experimentation.

In sum, in view of the guidance in the specification and knowledge in the art regarding Factor IX structure and function, and the fact that the specification exemplifies Factor IX in which binding to collagen IV is reduced, one skilled in the art could make and use the claimed compositions without undue experimentation. Accordingly, claims 1 to 4 and 6 to 9 are adequately enabled and, as such, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §102(e) and 103(a)

The rejection of claims 1 to 3 and 6 to 8 under 35 U.S.C. §102(e) as allegedly anticipated by Wilson *et al.* (U.S. Patent No. 5,866,552) is respectfully traversed. The Examiner asserts that

the previously filed Declaration under 37 C.F.R. §1.131 was not signed by all of the inventors of the application.

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ 2d 1655 (Fed. Cir. 1990), *In re Bond*, 15 USPQ 2d 1566 (Fed. Cir. 1990).

Submitted herewith is a Declaration under 37 C.F.R. §1.131 executed by Dr. Roland W. Herzog (Exhibit 1). Accordingly, as the Declaration under 37 C.F.R. §1.131 has been executed by all of the inventors of the application, Applicants respectfully request that the rejection under 35 U.S.C. §102(e) be withdrawn.

The rejection of claim 9 under 35 U.S.C. §103(a) as allegedly unpatentable over Weiner in view of Crabtree *et al.* is respectfully traversed. The Examiner indicates that claim 9 remains rejected for the reasons of record, since it is directed to a "vector" of claim 1.

Claim 1, as amended, recites "virus." Accordingly, in view of the amendment, Applicants respectfully request that the rejection of claim 9 under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1 to 4 and 6 to 9 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 03-3975.

Respectfully submitted,

Date: 5.18.04

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	High *et al.*	Art Unit:	1636
Serial No.:	09/393,844	Examiner:	Sullivan, DM.
Filed:	September 10, 1999		
Title:	METHODS AND COMPOSITIONS FOR USE IN GENE THERAPY FOR TREATMENT OF HEMOPHILIA		

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 C.F.R. §1.131

Dear Sirs:

I, Dr. Roland W. Herzog, do hereby declare and state that:

1. I am a co-inventor of the subject matter described and claimed in United States Patent Application Serial No. 09/393,844, filed September 10, 1999, entitled: "METHODS AND COMPOSITIONS FOR USE IN GENE THERAPY FOR TREATMENT OF HEMOPHILIA".

2. I am familiar with the prosecution history of Application Serial No. 09/038,910.

3. I understand that the Examiner has cited Wiener *et al.* (WO96/15777) under 35 U.S.C. §102(a), Wilson *et al.* (U.S. Patent No. 5,866,552) under 35 U.S.C. §102(e), Skulimowski *et al.* (Methods in Molecular Genetics 7:3 (1995)) under 35 U.S.C. §103(a) and Thiell *et al.* (U.S. Patent No. 5,817,784) under 35 U.S.C. §103(a) against the claims of Application Serial No. 09/393,844.

EXHIBIT 1

4. I submit that Wiener *et al.*, Wilson *et al.*, Skulimowski *et al.* and Thiell *et al.* are not available as prior art under 35 U.S.C. §§102 or 103.

5. Prior to the publication date of Wiener *et al.*, Wilson *et al.*, Skulimowski *et al.* and Thiell *et al.* the recombinant AAV vector including DNA encoding Factor IX was first constructed by me or under my direction at the Children's Hospital of Philadelphia, Philadelphia, Pennsylvania. We were diligent from the time that we first discussed and conceived the invention with respect to the Factor IX AAV vector, reduced to practice the Factor IX AAV vector, and up until the time of filing the patent application.

6. Evidence of the conception and reduction to practice of the present invention is supplied in the form of a copy of a page from our laboratory notebooks (Exhibit 2), prior to October 3, 1995, the publication date of Skulimowski *et al.*, the earliest published reference of Wiener *et al.*, Wilson *et al.*, Skulimowski *et al.* and Thiell *et al.* This page shows our reduction to practice of the recombinant AAV vector including DNA encoding Factor IX.

7. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

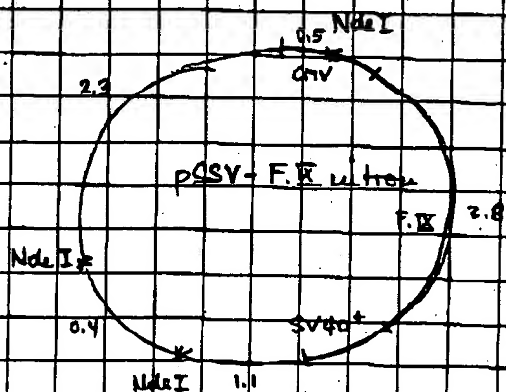
Date: 01-26-04

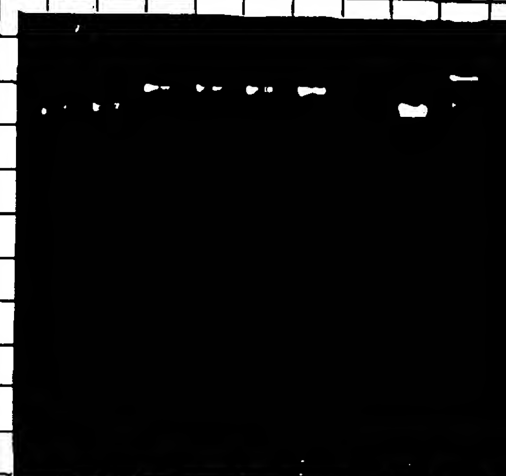
Dr. Roland W. Herzog, Ph.D.

EXHIBIT 1

pCEP-F.IX intron	30 µl	pAd-Bgl II	5 µl
10x	5 µl	10x	3 µl
Sal I	5 µl	Bgl II	3 µl
H_2O	10 µl	H_2O	19 µl

- made 3.2% sodium-citrate solution to anti-coagulate mouse blood (1.6 g sod. citrate / 50 ml)





①		②	
	0.4 kb		0.4 kb
	2.8 kb		1.6 kb
	4.9 kb		6.1 kb

- 293 cells (+ HeLa's) in 96-well plate: inf with Ad-lacZ (volume 50 µl) (19:30)

Ⓐ Ad-lacZ 1.5 x 10^12 part / ml (1.5 x 10^9 part. / µl)

① 200 µl DMEM 2% FBS + 3 µl Ad-lacZ
② ~~150 µl~~ 75 µl -"- + ~~50 µl~~ 25 µl ① ≑ (1/4 of ①)
③ ~~150 µl~~ 75 µl -"- + ~~50 µl~~ 25 µl ②

Ⓑ Ad-lacZ 1.5 x 10^10 part / ml (1.5 x 10^7 part. / µl)

① 180 µl DMEM 2% FBS + 20 µl Ad-lacZ
② 70 µl -"- + 70 µl ① ≑ (1/2 of ①)
③ 70 µl -"- + 70 µl ②

EXHIBIT 2